Docket No. MCP-284

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	SZYMCZAK et al.
Serial No.	:	09/966,441
Filed	:	09/28/2001
Title	:	SIMETHICONE SOLID ORAL DOSAGE FORM
Art Unit	:	1614
Examiner	:	Kwon, Brian Yong S.

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December 18, 2003

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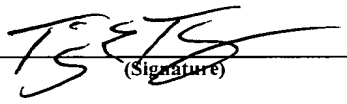
(Name of applicant, assignee, or Registered Representative)



(Signature)

December 18, 2003

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Mail-Stop AF
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APPEAL BRIEF

Dear Sir:

In accordance with the provisions of 37 CFR § 1.191, a timely Notice of Appeal was filed in the captioned application on August 29, 2003. A petition for a two-month Extension of Time is submitted concurrently herewith. Accordingly, this Appeal Brief is timely filed, with an executed Certificate of Mailing on or before January 2, 2004. Three copies of the Appeal Brief are enclosed.

1) Real Party in Interest

The real party in interest in the application in this appeal is Applicants' assignee McNeil-PPC, Inc., a corporation of New Jersey, a wholly owned subsidiary of Johnson & Johnson, a New Jersey corporation.

(2) Related Appeals and Interferences

No related appeals or interferences are known to exist.

(3) Status of the Claims

Claims 1-14 and 16-28 are the claims on appeal, a copy of which are attached hereto in the Appendix to this Brief. Claims 6, 18, and 27-28 have been withdrawn. No claims stand allowed in this application.

(4) Status of Amendments

The Amendment submitted in Paper No. 11 was entered in the captioned application according to Paper No. 12, dated October 1, 2003.

(5) Summary of the Invention

The present invention provides a composition for forming a compressed solid dosage form that is a free-flowing compressible admixture of simethicone, an adsorbent, and an optional active agent, wherein the weight ratio of simethicone to adsorbent is at least about 1:2.22. Also included are solid dosage forms made from a free-flowing compressible admixture of simethicone, an adsorbent, and an optional active agent, wherein the weight ratio of simethicone to adsorbent is at least about 1:2.22.

(6) Issues on Appeal

(A) Whether matter cancelled in the specification is new matter under 35 USC § 132.

(B) Whether amendments to the inventions of claims 1-5, 7-12, 14, and 26 continue to allegedly fail to comply with the written description requirement under 35 USC § 112, first paragraph.

(C) Whether the inventions of claims 1-2 and 4-5 are unpatentable under 35 U.S.C. §102(b) as being anticipated by Stevens et al. (US Pat. No. 5,679,376).

(D) Whether the inventions of claims 1-2, 4-5, 7-8 and 11-12 are unpatentable under 35 U.S.C. §102(b) as being anticipated by Luber et al (US Pat. No. 6,103,260).

(E) Whether the inventions of claims 3, 9-10, 13-14, and 19-26 are unpatentable under 35 USC § 103(a) over Kitsusho Yakuhim Kogyo KK (JP 398241) in view of Tobyn et al. (International Journal of Pharmaceutics 169(1998) 183-194).

(F) Whether the inventions of claims 16 and 17 are unpatentable under 35 USC § 103(a) over Kitsusho Yakuhim Kogyo KK (JP 398241) in view of Tobyn et al. (International Journal of Pharmaceutics 169(1998) 183-194) and Stevens et al. (US Pat. No. 5,679,376).

(7) Grouping of Claims

It is believed that all of the pending claims are patentable over the rejection made by the Examiner. For purposes of this Appeal, claims 1-5, 7-12, and 25 stand together as Group A and claims 13-14, 15-17, 19-24, and 26 stand together as Group B.

(8) Argument

While the October 1, 2003 Advisory Action (Paper No. 12) entered the amendments from Paper No. 11 for purpose of appeal, there was no written explanation as to how the new or amended claims would be allowed, objected to, or rejected. Therefore, it is presumed for purposes of this appeal that the previous objections and rejections remain. It is based on this presumption that the following Argument is presented.

Objection to the Specification

The Examiner objected to the explicit disclosure of the quotient obtained by the ratio of simethicone to adsorbent. (Paper No. 9 at 3.) In particular, the Examiner contended that the quotients were "not supported by the original disclosure." The Examiner reasoned that the term "'at least about 1:2.22' relates to the range of weight ratio of simethicone to adsorbent, for example 1:2.20, 1:2.21, 1:2.22, 1:2.23, 1: 2.24,

1:2.25, 1:2.26, 1:2.27, 1:2.28, etc." (*Id.* at 4.) The Examiner further reasoned that a ratio of 1:1.111 "does not fall within "at least 1:2.22", nor "at least about 1:1.80, nor "at least 1 part simethicone to 1.75 parts adsorbent." (*Id.*) The Examiner applied similar reasoning to "at least about 0.5", "at least about 0.56", and "at least about 0.57." (*Id.*) The Examiner then required cancellation of the alleged new matter. (*Id.*)

While not agreed with for the reasons already of record, the offending quotients added in the January 31, 2003 Response were cancelled in Paper No.11 and it was believed at that time to have made this objection moot. However, the October 10, 2002 Advisory Action (Paper No. 12) was silent as to the status of this objection. It is again submitted that this objection is moot and should be withdrawn.

(i) Rejections under 35 USC § 112, first paragraph

Claims 1-5, 7-12, 14, and 26 (Group A) were rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. (Paper No. 9 at 5.) The Examiner contended that "the claim(s) contain subject matter that was not described in the specification in such a way to convey that to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. (*Id.*) In making the rejection, the Examiner asserted that "[the reasoning of this rejection has been discussed in above new matter objection under 35 USC § 132." (*Id.*)

While not agreed with for the reasons already of record, the offending quotients added in the January 31, 2003 Response were cancelled in claims 1-5, 7-12, 14, and 26 in Paper No.11 and it was believed at that time to have made this objection moot. However, the October 10, 2002 Advisory Action (Paper No. 12) was silent as to the status of this objection. It is again submitted that this rejection is moot and should be withdrawn.

Anticipation Rejection

Claims 1-2 and 4-5 were rejected under 35 USC §102(b) as anticipated by Stevens, US Patent No. 5,679,376, ("Stevens"). (OA at 5.)

For the reasons set forth below, the rejection, respectfully is traversed.

Stevens discloses

A solid oral dosage form for the treatment of gastrointestinal disorders comprising a therapeutically effective amount of a pharmaceutical suitable for the treatment of gastric disorders selected from the group consisting of cimetidine, ranitidine, famotidine, diphenoxylate, loperamide, loperamide-N-oxide, pharmaceutically acceptable salts thereof and combinations thereof; and a therapeutically effective amount of simethicone wherein the pharmaceutical and simethicone

(Abstract)

FIG. 6 provides dissolution profiles for three formulations of uncoated loperamide present with simethicone provided in an admixed single solid oral dosage form. The solid line indicates the dissolution profile of loperamide from a solid dosage form comprised of Simethicone GS-J (40% simethicone adsorbed onto a diluent) and uncoated granules containing loperamide. The dashed line indicates the dissolution profile of loperamide from a second solid dosage form containing granules of Simethicone GS-J (40% simethicone adsorbed onto a diluent) and uncoated granules containing loperamide. The dotted line indicates the dissolution profile of loperamide from a third solid dosage form containing granules of Simethicone GS-J (40% simethicone adsorbed onto a diluent) and uncoated granules containing loperamide. The formulations for these solid dosage forms are contained in Example I.

(Col. 2, lns. 40-55.)

The simethicone used in the present invention can be Simethicone USP or a commercially prepared granulation such as Simethicone GS (30% Simethicone USP adsorbed onto maltodextrins available from Union Carbide) or Simethicone GS-J (40% Simethicone USP adsorbed onto maltodextrins available from Union Carbide). The amount of simethicone contained in the solid dosage form should be sufficient to provide a therapeutic dosage to a patient suffering from gas or diarrhea and its associated symptoms. The preferred dosage ranges for simethicone is in the range of about 20 mg to about 125 mg per dosage unit, generally not to exceed 500 mg/day. The dosage ranges may vary for age and weight of a patient as well as the severity of symptoms.

(Col. 4, lns. 31-43.)

Ingredient	Mg/Tablet
Simethicone, USP	125.0
Dibasic Calcium Phosphate, USP	370.0
Microcrystalline Cellulose, NF	265.5
Colloidal Silicon Dioxide, NF	31.5
Sodium Starch Glycolate, NF	72.0
Croscarmellose Sodium, NF	36.0
Loperamide HCl, USP	2.0
Total	902.0

DIRECTIONS: .

The third experimental tablet was manufactured in the following manner:

1. Mix loperamide HCl, dibasic calcium phosphate and microcrystalline cellulose in a planetary mixer (Hobart mixer) for 30 seconds.
2. Granulate by adding simethicone into Step 1 for 1 minute.
3. While mixing add colloidal silicon dioxide to Step 2 for 2.5 minutes.
4. Add sodium starch glycolate and croscarmellose sodium and mix for 1 minute.
5. Compress the tablets as set forth above for the first experimental tablet.

FIG. 5 shows the dissolution profile of simethicone and loperamide when provided in separate solid oral dosage form. As is shown in FIG. 6, the dissolution profile of loperamide in tablets containing both loperamide and simethicone in a single solid oral dosage form was reduced to the point that almost no loperamide was detected. The solid, dashed and dotted lines in FIG. 6 represent the dissolution profiles for the first, second and third experimental tablets, respectively. These results demonstrate the need for a new solid oral dosage form containing a combination of simethicone and a pharmaceutical suitable for the treatment of a gastric disorders.

In making the rejection, the Examiner merely stated that "[t]his rejection is analogous to the original rejection." (Paper No. 9 at 5.) In the original rejection, the Examiner contended only that "Stevens teaches a solid oral dosage form comprising loperamide, simethicone, microcrystalline cellulose and colloidal silicone dioxide,

wherein a ratio of simethicone and microcrystalline cellulose is about 1.2.12 (125 mg :265.5 mg) or a ratio of simethicone and a combination of colloidal silicon dioxide and microcrystalline cellulose is about 1:2.37 (125 mg:297 mg). (Paper No. 5 at 5.) The Examiner appears to have taken official notice that the use of microcrystalline cellulose and colloidal silicon dioxide were inherently adsorbents. Further, the Examiner concluded that since the calculated ratio of 1:2.12 (simethicone to microcrystalline cellulose) or 1 2.37 (simethicone to the combination of microcrystalline cellulose and colloidal silicon dioxide) fell within the claimed ration of simethicone to adsorbent of at least about 1:2.22 (claim 1) and at least 1:2. (*Id.*)

As is well settled, anticipation requires "identity of invention." Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim.

We note that the Examiner asserted that dibasic calcium phosphate "falls within the broadly defined adsorbent." (Paper No. 5 at 6-7.) The example relied upon by the Examiner in the instant rejection discloses using 370 mg of dibasic calcium phosphate, USP. It appears that the Examiner may have overlooked this fact in making the instant rejection.

Relying on this fact, it appears that Stevens does not disclose as much as the Examiner asserted. For example, the sole example in Stevens relied on by the Examiner provides factual evidence that the ratio of simethicone to adsorbent (dibasic calcium phosphate + microcrystalline cellulose + colloidal silicon dioxide) is 125:667, or 1:5.34. It is submitted that a ratio of 1:5.34 does not fall within the scope of the claimed subject matter as properly interpreted in view of doctrine of claim differentiation. For this reason, the rejection is improper and should be withdrawn.

Because claims 2, 4, and 5 depend from claim 1, the rejection to these claims based on Stevens is also improper and should be withdrawn.

Claims 1-2, 4-5. 7-8, and 11-12 were rejected under 35 USC §102(b) as anticipated by Luber et al., US Patent No. 6,103,260, ("Luber"). (Paper No. 9 at 5.)

For the reasons set forth below, the rejection respectfully is traversed.

Luber discloses

In accordance with the present invention, the simethicone is admixed with the granulated anhydrous tribasic or dibasic calcium phosphate to form a uniform free flowing granular composition. Generally, it is desired that the admixture contain a proportionate amount of the simethicone antifoam agent and granular anhydrous calcium phosphate which is consistent with forming a free-flowing granular composition. Preferably, the proportionate amounts of the ingredients of the granular admixture composition is about 10–70% w/w simethicone and about 30–90% w/w granular anhydrous tribasic or dibasic calcium phosphate. The ingredients (Col. 3, lns. 31-41.)

Optionally, the dosage form can include one or more additional active ingredients suitable for the treatment of gastrointestinal disorders, for example heartburn, ulcers or diarrhea. Suitable active agents for treating gastrointestinal disorders include heartburn or antiulcer medicaments such as sucralfate, the H2 receptor antagonists cimetidine, ranitidine, famotidine or nizatidine, proton pump inhibitors such as omeprazole or lansoprazole; antidiarrheal agents such as loperamide and diphenoxylate; gastrointestinal motility agents such as cisapride, and antacids such as aluminum hydroxide, magnesium carbonate, magnesium hydroxide, calcium carbonate and the like. The amount of such additional active ingredient combined with the simethicone should be an amount sufficient to provide a therapeutic dosage to a patient suffering from the gastrointestinal disorder being treated. (Col. 5, lns. 13-28.)

EXAMPLE 1

Preparation of Simethicone/Granular Anhydrous Tribasic Calcium Phosphate Admixture

1. 700 gm of granular tricalcium phosphate (Tritab®, Rhone-Poulenc, Shelton, Conn.) is added to the mixing bowl of a Kitchen Aid mixer.
2. While mixing at low speed, over a period of 5 minutes add 200 gm of simethicone, USP.
3. Continue mixing at low speed for an additional 5 minutes.
4. Add 2.5 gm of silicon dioxide and mix an additional 5 minutes.

This intermediate is a free flowing granulation with no large agglomerates. (Col. 5, lns. 31-44.)

EXAMPLE 2

Preparation of Simethicone/Granular Anhydrous Dibasic Calcium Phosphate Admixture

1) 700 gm of granular anhydrous dibasic calcium phosphate, (Emcompress® Anhydrous, Mendell, Paterson, N.J.) is added to the mixing bowl of a Kitchen Aid mixer.
2) While mixing a low speed, over a period of 5 minutes add 200 gm of simethicone, USP.
3) Continue mixing at low speed for an additional 5 minutes.
4) Add 7.5 gm of silicon dioxide and mix an additional 5 minutes.

This intermediate is a free flowing granulation with no large agglomerates.

(Col. 5, lns. 45-59.)

EXAMPLE 4

Preparation of Chewable Tablets Containing Simethicone/Granular Anhydrous Tribasic Calcium Phosphate Admixture

1) 1500 gm of tricalcium phosphate powder was dry granulated by roller compacting at a roll pressure of 500 psi.
2) The compact was passed through a Fitz Mill with a 0.093" screen, knives forward.
3) The milled material was screened, and the -30 to +80 mesh fraction collected as product.
4) 700 gm of compacted tricalcium phosphate granules was added to the mixing bowl of a Kitchen Aid mixer.
5) While mixing a low speed, over a period of 5 minutes add 200 gm of simethicone, USP.
6) Continue mixing at low speed for an additional 5 minutes.
7) Add 20 gm of tricalcium phosphate powder and mix an additional 5 minutes.

This intermediate is a free flowing granulation with no large agglomerates.

8) 91 gm of the above intermediate was then blended with 98 gm of Dextrates, 7.5 gm granular sorbitol, 0.6 gm peppermint flavor, and 0.5 gm stearic acid.
9) The blend was finally compressed using ⅝" FFBE tooling. The tablet weight was 1300 mg. The physical properties of the tablet were:

Hardness: 11–12 kp

Friability: less than 0.1% at 100 drops

Disintegration in N/10 HCl: less than 1.5 minute

Defoam: 7 secs

(Col. 6, lns 28-58.)

EXAMPLE 6

Preparation of Swallowable Film Coated Tablets Containing Simethicone/Granular Anhydrous Tribasic Calcium Phosphate Admixture

Ingredient	Qty mg/tab
PART I - concentrate	
Tribasic calcium phosphate, NF, Anhydrous, granular	500
Simethicone, USP	25
Tribasic calcium phosphate, NF, Anhydrous, Powder	25
PART II- Scavenger	
Tribasic calcium phosphate, NF, Anhydrous, Powder	20
PART III- Excipient/Binder system	
Dibasic calcium phosphate, Dihydrate, USP	105.75
Microcrystalline cellulose, NF (MCC)	50
Crystalline sorbitol, NF	70
Croscarmellose sodium, NF	30
PART IV-Lubricant	
Magnesium Stearate, NF	0.5

PART 1) A concentrate comprised of granular and powdered anhydrous tribasic calcium phosphates, and simethicone is prepared by adding simethicone compound, USP to a moving bed of granular tribasic calcium phosphate so that the simethicone is distributed evenly and the granular calcium phosphate particle size remains essentially unchanged. The bed is kept in motion by low shear mixers such as fluid bed, Nauta, PK without intensifier bar, pin mixer, or ribbon mixer. After the bed has adsorbed the simethicone, anhydrous tribasic calcium phosphate powder is added. The granulation may then be screened through a No. 20 US Std screen (~840 micron).

PART 2) When a final blend for compression is desired an additional quantity of calcium phosphate powder is added to the PART 1 concentrate and blended.

PART 3) Excipients including a disintegrant are then added with low shear blending which imparts uniform distribution of the active within a binding matrix of limited compositional range.
PART 4) The final addition step is to add a lubricant.
PART 5) The blend is compressed into tablets using a rotary tablet press.
PART 6) Tablets are then film coated and/or gelatin dipped.
Typical film coated tablet characteristics:
Hardness range: 6–14 kp
Tablet weight (core): Approx. 1000 mg
USP disintegration time in water : Less than 7 minutes, in acid media : Less than 6 minutes
USP Defoaming activity time: 9 seconds (Col. 7, line 26 – col. 8, line 13.)

In making the rejection, the Examiner merely stated that "[t]his rejection is analogous to the original rejection." (Paper No. 9 at 5.) In the original rejection of claims 1-2, the Examiner asserted that "Luber teaches an antifoam oral solid dosage form preparations formed from a free [f]lowing granular composition comprising an admixture of simethicone and [] either one or both of granular anhydrous tribasic calcium phosphate or dibasic calcium phosphate, wherein the simethicone is adsorbed by the granular anhydrous tribasic or dibasic calcium phosphate or mixture thereof, and where ratios of simethicone to granular tricalcium phosphate are 1:3.5 in Examples 1-2 and 1:4 in Example 6. (OA at 6.) The Examiner further asserted "[a]lthough Luber is silent about the use of granular tribasic calcium phosphate or dibasic calcium phosphate as an adsorbent" such compounds "read[] on the broadly defined term "adsorbent." Based upon this, the Examiner concluded that "the reference clearly anticipates the claimed invention" because "the claimed weight ratio of simethicone to adsorbent" encompasses the weight ratio of simethicone to tribasic calcium phosphate or dibasic calcium phosphate disclosed in Luber.

As is well settled, anticipation requires "identity of invention." Each and every element recited in a claim must be found in a single prior art reference and arranged as in the claim.

It appears that Luber does not disclose as much as the Examiner asserted. For example, the Examiner asserted that the ratios of simethicone to granular tricalcium

phosphate were 1:3.5 in Examples 1-2 and 1:4 in Example 6. It is submitted that a ratio of about 1:3.5 and 1:4 do not fall within the scope of the claimed subject matter as properly interpreted in view of the doctrine of claim differentiation. For this reason, the rejection is improper and should be withdrawn.

Because claims 2, 4-5. 7-8, and 11-12 depend from claim 1 under the doctrine of claim differentiation, the rejection to these claims based on Luber is also improper and should be withdrawn.

(iv) Rejection under 35 USC § 103

Claims 3, 9-10, 13-15, and 19-26 were rejected under 35 USC §103(a) as being unpatentable over Kitsusho Yakuhin Kogyo KK (JP 398241) ("Kitsusho") in view of Tobyn et al, (International Journal of Pharmaceutics 169 (1998) 183-194) ("Tobyn") (OA at 9.)

For the reasons set forth below the rejection, respectfully is traversed.

Kitsusho discloses a method for preparing simethicone tablets by mixing and granulating simethicone with aluminum silicate, magnesium aluminum metasilicate, and magnesium silicate. (p. 2.) In particular, the formulation disclosed by the above Japanese patent requires at most 25 % simethicone and 75% or greater silicate, binder and dispersing agent. Binders were disclosed as being starch and lactose. Dispersing agent was disclosed as being carboxymethylcellulose. Further, Kitsusho discloses that when the amount of simethicone exceeds 25%, a portion of the simethicone can be carried away, therefore the tablet workability is not desirable.

Tobyn discloses a comparison between microcrystalline cellulose ("MCC") and silicified microcrystalline cellulose ("siMCC"). According to Tobyn, MCC has properties such as low bulk density, high lubricant sensitivity, poor flow characteristics, and influence of moisture on the compression characteristics. (Tobyn at 183.) Tobyn disclosed that surface treatment of MCC with silicon dioxide or silicic acid had beneficial characteristics with respect to disintegration and mechanical resistance. (Tobin at 184.) Tobyn also discloses that siMCC was chosen to possess a number of pharmaceutical advantages in terms of powder flow, tablet strength, lubricant sensitivity and we granulation. (Tobyn at 184.) Tobyn disclosed making a dry mix using Emcocel 90 M and dried silica and a wet mix was made using Emcocel 90 M with colloidal silica

dispersion, which was tray dried and milled. (Tobyn at 184-85.) Tobyn concluded that no bulk chemical changes in MCC occurred with converted to siMCC. (Tobyn at 193.) Tobyn went on to postulate that "[t]he fundamental chemical properties of the novel material are very similar to the parent material." (Tobyn at 193.) Tobyn also disclosed that siMCC had improved functionality in terms of improved bulk physical properties and mechanical characteristics due to some other intrinsic property rather than a change in the base chemical parameters of the novel material. (*Id.*)

In addition, at page 191, Tobyn discloses that, among other things, "[t]he values obtained relating to the total pore areas, the median pore diameters and the porosities of the samples ... pore sizes were found to be very similar ... it is interesting to that there is no apparent increase in accessible surface area with the SMCC90 sample, whereas there is with dry mixes of silicon dioxide and MCC."

In making the rejection, the Examiner merely stated that "[t]his rejection is analogous to the original rejection." (Paper No. 9 at 6.) In the original rejection, the Examiner asserted that Kitsusho teaches "teaches a method for preparing simethicone tablets by mixing and granulating simethicone with magnesium aluminum metasilicate. (Paper No. 5 at 9.) The Examiner further asserted that the "formulation disclosed by Kitsusho requires at most 25% simethicone and 75% or greater silicate, binder (i.e., starch and lactose) and dispersing agents (i.e., carboxymethylcellulose)." (Paper No. 5 at 9-10.) The Examiner also contended that " [Kitsusho] teaches that when the amount of simethicone exceeds 25% there is a tendency that a portion of the simethicone can be carried away, therefore the tablet workability is not desirable." (Paper No. 5 at 10.) The Examiner acknowledged, however, that Kitsusho differs from the presently claimed invention in that:

1. the incorporation of silicified microcrystalline cellulose in said composition;
2. at least 30 wt% simethicone in said composition;
3. the specific amounts of silicified microcrystalline cellulose and magnesium aluminometasilicates in said composition; and
4. the specific har[d]ness of value of the tablet. (Paper No. 5 at 10.)

To fill the acknowledged gap, the Examiner relied upon Tobyn as disclosing the advantage of using silicified microcrystalline cellulose in improving tablet workability such as "powder flow," "tablet strength," "lubricant sensitivity" and "wet granulation." (*Id.* at 10.)

The Examiner then concluded that "[t]o incorporate such teaching into the teaching of Kitsusho, would have been obvious in view of Tobyn, who teaches the advantage of using silicified microcrystalline cellulose as a pharmaceutical excipient [] to improve powder flow characteristics, lubricant sensitivity, tablet strength and better bulk physical properties. (*Id*). The Examiner reasoned that that "[o]ne having ordinary skill in the art would have been motivated, with a reasonable expectation of success, to incorporate silicified microcrystalline cellulose having good free-flowing and disintegrating properties (which is relatively new pharmaceutical excipients in the art) such that the table workability would be significantly improved. (*Id.*) The Examiner reasoned further "one having ordinary skill in the art would have been motivated to increase the amount of simethicone above 25% in the solid final blend for tableting by incorporating silicified microcrystalline cellulose in said composition." (Paper No. 5 at 10-11.)

The Examiner then asserted that "[a]lthough the prior art references are silent about the specific dosage amounts of active ingredients and the hardness value of tablet, the optimization of [known] active and inactive ingredients in a composition or the determination of optimum hardness value of the tablet is well considered within the skill of the artisan, absent evidence to the contrary."

Obviousness, cannot be based upon speculation. Nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." When a conclusion of obviousness is not based upon facts, it cannot stand.

"Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed. Cir. 1998). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements,

and to combine them as combined by the inventor. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); ATD Corp, 159 F.3d at 546, 48 USPQ2d at 1329; Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.").

As to the Group A claims, the rejection uses Tobyn to fill in the acknowledged gaps in Kitsusho, but it does not appear that the Examiner considered all of Tobyn's disclosure in making the rejection. For example, Tobyn discloses that, among other things,

> "[t]he values obtained relating to the total pore areas, the median pore diameters and the porosities of the samples ... pore sizes were found to be very similar ... it is interesting to that there is no apparent increase in accessible surface area with the SMCC90 sample, whereas there is with dry mixes of silicon dioxide and MCC." (Tobyn at 191.)

It is not seen where the record provides any motivation or suggestion to use SMCC90 over MCC to increase loading, especially where there was no increase in accessible surface area. Because the record provides no expectation of success, the rejection is improper and should be withdrawn.

As to the Group B claims, the rejection also fails to point out where in Tobyn even one experiment using simethicone is disclosed. The rejection then summarily concludes that one having ordinary skill in the art would have been motivated to increase the amount of simethicone above 25% in the solid final blend for tableting by incorporating silicified microcrystalline cellulose in said composition. However, the rejection does not support such a conclusion. It is not seen where in the rejection the Examiner provided any facts in Tobyn to indicate that simethicone, a viscous oil-like substance, could be adsorbed onto silicified microcrystalline cellulose, much less any facts indicating that silicified microcrystalline cellulose would have the same improved properties when formulated with simethicone. Thus, for this additional reason, the rejection is not supported by fact and must be withdrawn for this reason alone.

Also applicable to the Group B claims, the Examiner has not provided any facts to support the proposition that using siMCC in Kitsusho's formulation would overcome the

problem acknowledged by Kitsusho, e.g., not exceeding 25% simethicone in the formulation. It is not seen where there are any facts in the rejection to suggest any expectation of success for increasing the amount of simethicone in a formulation using an additional adsorbent, e.g., siMCC. Because it appears that the rejection is based upon possibilities or probabilities, it is improper and should be withdrawn.

Claims 16 and 17 were rejected under 35 USC §103(a) as being unpatentable over Kitsusho in view of Tobyn and Stevens. (OA at 11.)

For the reasons set forth below the rejection, respectfully is traversed.

The disclosures of Kitsusho, Tobyn, and Stevens set forth above are herein incorporated by reference.

In making the rejection, the Examiner merely stated that "[t]his rejection is analogous to the original rejection." (Paper No. 9 at 6.) In the original rejection, the Examiner asserted that "the modified teach of Kitsusho includes all that is recited in claims 16 and 17 except for the incorporation of active pharmaceuticals such as famotidine. (Paper No. 5 at 11.) To fill the acknowledged gap, the Examiner relied on Stevens as "teach[ing] or suggest[ing] the use of simethicone and other pharmaceutical excipients in preparing oral solid dosage form containing H2 blockers (e.g., famotidine). (Paper No. 5 at 11.)

The Examiner contended that "[o]ne having ordinary skill in the art would have know that simethicone is routinely combined with H2 blockers such as famotidine in solid oral dosage formulation art, and would have been further motivated to further modify the teaching of Kitshusho such that the better solid dosage form containing famotidine would be formulated. (Paper No. 5 at 11.) The Examiner reasoned "[o]ne having ordinary skill in the art would have been motivated to do this so that the tablet workability would be significantly improved." (Paper No. 5 at 11.)

Obviousness, cannot be based upon speculation. Nor can obviousness be based upon possibilities or probabilities. Obviousness ***must*** be based upon facts, "cold hard facts." When a conclusion of obviousness is not based upon facts, it cannot stand.

"Determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention." ATD Corp. v. Lydall, Inc., 159 F.3d 534, 546, 48 USPQ2d 1321, 1329 (Fed.

Cir. 1998). There must be a teaching or suggestion within the prior art, within the nature of the problem to be solved, or within the general knowledge of a person of ordinary skill in the field of the invention, to look to particular sources, to select particular elements, and to combine them as combined by the inventor. See Ruiz v. A.B. Chance Co., 234 F.3d 654, 665, 57 USPQ2d 1161, 1167 (Fed. Cir. 2000); ATD Corp, 159 F.3d at 546, 48 USPQ2d at 1329; Heidelberger Druckmaschinen AG v. Hantscho Commercial Prods., Inc., 21 F.3d 1068, 1072, 30 USPQ2d 1377, 1379 (Fed. Cir. 1994) ("When the patented invention is made by combining known components to achieve a new system, the prior art must provide a suggestion or motivation to make such a combination.").

The rejection uses, among other things, Tobyn to fill in the acknowledged gaps in Kitsusho, but it does not appear that the Examiner considered all of Tobyn's disclosure in making the rejection. For example, Tobyn discloses that, among other things,

> "[t]he values obtained relating to the total pore areas, the median pore diameters and the porosities of the samples ... pore sizes were found to be very similar ... it is interesting to that there is no apparent increase in accessible surface area with the SMCC90 sample, whereas there is with dry mixes of silicon dioxide and MCC." (Tobyn at 191.)

It is not seen where the record provides any motivation or suggestion to use SMCC90 over MCC to increase loading, especially where there was no increase in accessible surface area. It is not seen where Stevens addresses the lack of any expectation of success created by Tobyn. Because the record provides no expectation of success, the rejection is improper and should be withdrawn.

In addition, the rejection also fails to point out where in Tobyn even one experiment using simethicone is disclosed. The rejection then summarily concludes that one having ordinary skill in the art would have been motivated to increase the amount of simethicone above 25% in the solid final blend for tableting by incorporating silicified microcrystalline cellulose in said composition.

However, the rejection does not support such a conclusion. It is not seen where in the rejection the Examiner provided any facts in Tobyn to indicate that simethicone, a viscous oil-like substance, could be adsorbed onto silicified microcrystalline cellulose, much less any facts indicating that silicified microcrystalline cellulose would have the

same improved properties when formulated with simethicone. Thus, the rejection is not supported by fact and must be withdrawn for this reason alone.

Further, the Examiner has not provided any facts to support the proposition that using siMCC in Kitsusho's formulation would overcome the problem acknowledged by Kitsusho, e.g., not exceeding 25% simethicone in the formulation. It is not seen where there are any facts in the rejection to suggest any expectation of success for increasing the amount of simethicone in a formulation using an additional adsorbent, e.g., siMCC. Because it appears that the rejection is based upon possibilities or probabilities, it is improper and should be withdrawn.

Finally, Stevens does appear to close the gaps in the Examiner's rejection. The sole example in Stevens relied on by the Examiner provides factual evidence that the ratio of simethicone to adsorbent (dibasic calcium phosphate + microcrystalline cellulose + colloidal silicon dioxide) is 125:667, or 1:5.34. It is submitted that a ratio of 1:5.34 does not fall provide the requisite motivation to one of ordinary skill in the art to do what the Inventors of the captioned application have claimed. For this reason, the rejection is improper and should be withdrawn.

Accordingly, for the reasons set forth above, withdrawal of the rejections, and allowance of the claims is respectfully solicited

Respectfully submitted,

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APPENDIX

(9) Claims on Appeal

Claim 1. (previously presented): A composition for forming a compressed solid dosage form comprising a free-flowing compressible admixture of simethicone and an adsorbaent, wherein the weight ratio of simethicone to adsorbent is at least about 1:2.22.

Claim 2. (previously presented): A composition of claim 1, wherein the weight ratio of simethicone to adsorbaent is at least about 1:2.00.

Claim 3. (previously presented): A composition of claim 1, wherein the adsorbent comprises a combination of silicified microcrystalline cellulose and magnesium aluminometasilicate.

Claim 4. (original): A composition of claim 1, further comprising at least one additional active agent.

5. (previously presented): A composition of claim 4, wherein the active agent is selected from the group consisting of bisacodyl, famotidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

Claim 6. (withdrawn) A composition of claim 5, wherein the active agent is loperamide, or pharmaceutically acceptable salts, esters, or isomers thereof.

Claim 7. (original) A composition of claim 1 having at least 34% simethicone.

Claim 8. (original) A composition of claim 7, having from about 35wt% to about 54wt% simethicone.

Claim 9. (previously presented) A composition of claim 3 having from about 19 wt% to about 27 wt% silicified microcrystalline cellulose and having from about 31 wt% to about 39 wt% magnesium aluminometasilicate.

Claim 10. (original) A composition of claim 9 having from about 23 wt% to about 27 wt% silicified microcrystalline cellulose and from about 33wt% to about 37 wt% magnesium aluminometasilicate.

Claim 11. (original) A composition of claim 1, wherein the composition is compressed into a tablet having a hardness value of at least 2 kp/cm^2.

Claim 12. (original) A composition of claim 11, wherein the composition is compressed into a tablet having a hardness value of from about 5 to about 10 kp/cm^2.

Claim 13. (original) A solid oral dosage form comprising a compressed admixture of simethicone, silicified microcrystalline cellulose, and magnesium aluminometasilicate, wherein the simethicone is adsorbed on the silicified microcrystalline cellulose and magnesium aluminometasilicate.

Claim 14. (previously presented) A solid oral dosage form of claim 13, wherein the weight ratio of simethicone to silicified microcrystalline cellulose and magnesium aluminometasilicate is at least about 1:2.00.

Claim 15. (cancelled)

Claim 16. (original) A solid oral dosage form of claim 13, further comprising at least one additional active agent.

Claim 17. (previously presented) A solid oral dosage form of claim 16, wherein the active agent is selected from the group consisting of bisacodyl, famotidine, prucalopride, diphenoxylate, loperamide, lactase, mesalamine, bismuth, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.

Claim 18. (withdrawn) A solid oral dosage form of claim 17, wherein the active agent is loperamide, or pharmaceutically acceptable salts, esters, or isomers thereof.

Claim 19. (original) A solid oral dosage form of claim 13 having at least 30 wt% simethicone.

Claim 20. (original) A solid oral dosage form of claim 19, having from about 31 wt% to about 35 wt% simethicone.

Claim 21. (original) A solid oral dosage form of claim 13 having from about 19 wt% to about 27 wt% silicified microcrystalline cellulose and having from about 31 wt% to about 39 wt% magnesium aluminometasilicate.

Claim 22. (original) A solid oral dosage form of claim 21 having from about 23 wt% to about 27 wt% silicified microcrystalline cellulose and from about 33wt% to about 37 wt% magnesium aluminometasilicate

Claim 23. (previously presented) A solid oral dosage form of claim 13, wherein the compressed admixture is a tablet having a hardness value of at least 2 kp/cm^2.

Claim 24. (previously presented) A solid oral dosage form of claim 13, wherein the compressed admixture is a tablet having a hardness value of from about 5 to about 10 kp/cm^2.

Claim 25. (original) A composition for forming a solid dosage form comprising a free-flowing compressible admixture of simethicone, silicified microcrystalline cellulose, magnesium aluminometasilicate.

Claim 26. (previously presented) A compressed solid dosage form comprising an admixture of simethicone, silicified microcrystalline cellulose, magnesium aluminometasilicate, wherein the weight ratio of simethicone to silicified microcrystalline cellulose and magnesium aluminometasilicate is at least 1:2.00.

Claim 27. (withdrawn) A composition of claim 5, wherein the active agent is bisacodyl, or pharmaceutically acceptable salts, esters, or isomers thereof.

Claim 28. (withdrawn) A composition of claim 4, wherein the active agent is selected from the group consisting of acetaminophen, ibuprofen, naproxen, ketoprofen, cyclobenzaprine, meloxicam, rofecoxib, celecoxib, and pharmaceutically acceptable salts, esters, isomers, and mixtures thereof.